PATENT

Attorney Docket SMI-005.01

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By: Shirine Darvish
Shirine Darvish

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Isa Odidi and Amina Odidi	:	Paper No.:
Serial No.	09/166,701	:	Group Art Unit: 1617
Filed:	October 5, 1998	:	Examiner: Webman, Edward J.
For:	**Controlled Release Pharmaceutical Delivery Device and Process For Preparation Thereof**		

DECLARATION UNDER 37 C.F.R. 1.132

Box Fee Amendment
Commissioner for Patents
Washington, DC 20231

Isa Odidi and Amina Odidi declare that:

1. We are co-inventors of and are familiar with the present U.S. Patent Application Serial No. 09/166,701, and we are familiar with the Official Actions issued in the present application and the reference cited by the Examiner; U.S. Patent No. 4,610,870 to Jain *et al.*

2. The controlled release pharmaceutical device and the pharmaceutical composition of the present invention comprise, amongst other components, hydroxyethylcellulose and hydroxypropylmethyl cellulose.

3. U.S. Patent No. 4,610,870 to Jain *et al.* is directed to a controlled release pharmaceutical formulation containing a core portion. The core includes a medicament and a hydrocolloid gelling agent. The hydrocolloid may comprise cellulose polymers

which are cellulose ethers such as methyl cellulose, cellulose alkyl hydroxylates such as hydroxypropylmethyl cellulose, hydroxypropylcellulose, hydroxymethylcellulose or hydroxyethylcellulose.

4. In order to demonstrate that cellulose derivatives are not interchangeable with respect to the present invention, data is provided in Tables 1 and 2 for hydroxypropylmethyl cellulose (HPMC), ethylcellulose (EC), and hydroxyethylcellulose (HEC).

Table 1 Formulation of Model Drug using Different Cellulose Derivatives

Formulation	**HPMC 15%**	**HEC 15%**	**EC 15%**
Model Drug	50%	50%	50%
HPMC	15%	0%	0%
HEC	0%	15%	0%
EC	0%	0%	15%
Lactose	44%	44%	44%
Magnesium Stearate	1%	1%	1%

Table 2 Results from Dissolution studies of the Model Formulations

Time	HPMC 15%	HEC 15%	EC 15%
0	0	0	0
1	16.9	60	88.1
2	25	68	88.2
4	43	75.6	88.3
5	50	78.4	88.4
6	53.4	80	88.5
7	63.3	83.5	88.6
8	66.5	83.2	88.6
10	78.4	88.8	90
11	80.4	87.5	90
12	81.2	84.7	90
13	89.7	90	90
14	92	90	90

5. The amount of drug released in 1 hour is 17% for HPMC, 60% for HEC and 88% for EC. It was also observed that EC tablets broke up in 30 minutes. The time taken for 70% of the drug (i.e., $T_{70\%}$) to be released was about 9 hours for HPMC, 4 hours for HEC and 30 minutes for EC. These results clearly indicate that HPMC, HEC and EC are not interchangeable.

6. These results show that the release rates of the drug depends on the cellulose polymer used. Therefore, since these tests show that cellulosic polymers listed in U.S. Patent No. 4,610,870 to Jain *et al.* are not equivalent in combination with the present invention, one skilled in the art would not assume equivalency of the listed cellulose polymers in combination with the present invention.

7. Isa Odidi and Amina Odidi further declare that all statements made herein of his/her own knowledge are true and that all statements made on information and

belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

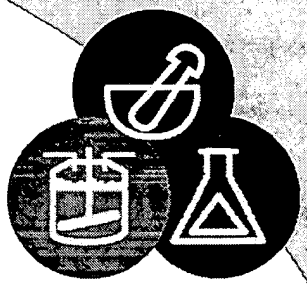
Respectfully submitted,

_____,2003 _____

Isa Odidi

_____, 2003 _____

Amina Odidi



Bulletin 3:

Nomenclature and Chemistry

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Pharmaceutical Polymers

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Nomenclature and Chemistry

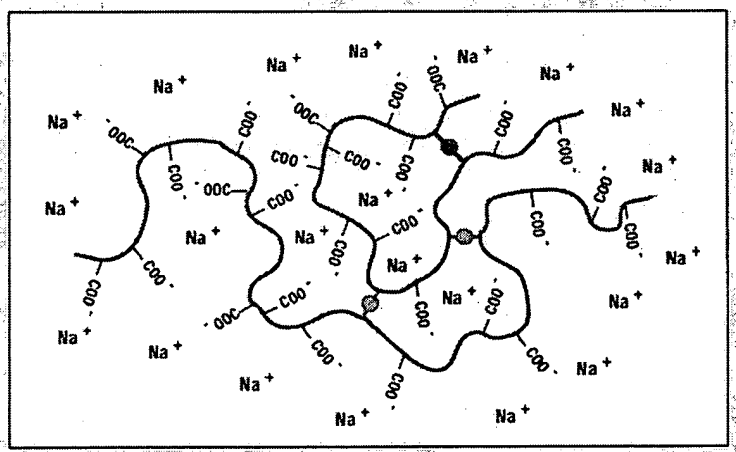
3.1 Overview

The USP-NF, European Pharmacopoeia, British Pharmacopoeia, United States Adopted Names Council (USAN), and International Nomenclature for Cosmetic Ingredients (INCI) have adopted the generic (i.e., non-proprietary) name "carbomer" for various Carbopol® homopolymer polymers. The Japanese Pharmaceutical Excipients list Carbopol homopolymers as "carboxyvinyl polymer" and "carboxy polymethylene." The Italian Pharmacopoeia also identifies Carbopol 934P as "carboxy polymethylene" and the Deutschen Artzneibuch calls Carbopol 980NF "polyacrylic acid." Carbopol copolymers, such as Carbopol 1342 NF and 1382, and the Pemulen® polymeric emulsifiers, have also been named "carbomer" by the USP-NF, but are considered "Acrylates/C10-C30 Alkyl Acrylates Crosspolymer" by the INCI. The Noveon® series of products is generically known as "polycarbophil."

The chemical composition and the chemical and physical properties of Noveon, Inc.'s pharmaceutical polymers suggest that they possess similar toxicological properties. All of these polymers have the same acrylic acid backbone. The main differences are related to presence of comonomer and crosslink density. With very minor adjustments in the crosslinker density and comonomer level, a large number of different polymers have been engineered to provide specific properties desired in end applications without substantially changing the gross molecular structure. Specifically, the polymers are either homopolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol (Carbopol homopolymers); homopolymers of acrylic acid crosslinked with divinyl glycol (Noveon polycarbophils); or copolymers of acrylic acid with minor levels of long chain alkyl acrylate comonomers crosslinked with allylpentaerythritol (Carbopol copolymers and Pemulen polymeric emulsifiers).

The molecular weight of these polymers is theoretically estimated to range from 700,000 to 3 or 4 billion. There are, however, no methods currently available to measure the actual molecular weight of a crosslinked (i.e. three-dimensional) polymer of this type. (See Section 3.2)

Figure 3.1.1
Dispersed Polymer in Donnan Equilibrium



Tabl 3.1.2

REGULATORY STATUS OF NOVEON INC.'s PHARMACEUTICAL POLYMERS

Product	USP 24/NF 19 Monograph	Other International Monographs	U.S. Drug Master File
Carbopol® 934 NF	Carbomer 934	JPE[1] British Pharmacopoeia	153
Carbopol 934P NF	Carbomer 934P	JPE[1] British Pharmacopoeia Italian Pharmacopoeia	153
Carbopol 940 NF	Carbomer 940	JPE[1] British Pharmacopoeia	153
Carbopol 971P NF	Carbomer 941	British Pharmacopoeia European Pharmacopoeia	7170[3]
Carbopol 71G NF	Carbomer 941	British Pharmacopoeia European Pharmacopoeia	7170[3]
Carbopol 974P NF	Carbomer 934P	British Pharmacopoeia European Pharmacopoeia	7170
Carbopol 980 NF	Carbomer 940	JPE[1] Deutschen Artzneibuch 10 European Pharmacopoeia	10072
Carbopol 981 NF	Carbomer 941	JPE[1] European Pharmacopoeia	10071
Carbopol 1342 NF	Carbomer 1342	JSCI[2]	7757
Carbopol 5984 EP		JPE[1] British Pharmacopoeia European Pharmacopoeia	153[3]
Pemulen® TR-1 NF	Carbomer 1342	JSCI[2]	7757[3]
Pemulen® TR-2 NF	Carbomer 1342	JSCI[2]	7757[3]
Noveon® AA-1 USP	Polycarbophil		7618
Noveon CA-1 USP	Calcium Polycarbophil		6542
Noveon CA-2 USP	Calcium Polycarbophil		6542

[1]JPE = Japanese Pharmaceutical Excipients

[2]JSCI = Japanese Standards for Cosmetic Ingredients

[3]These products have been added to the noted Drug Master File by Noveon, Inc.

Drug Master Files are reviewed annually and updated as needed.

Our manufacturing facilities are registered annually with the Food and Drug Administration (FDA).
The registration numbers are available upon request.

3.2 Molecular Weight of Carbopol® Polymers

3.2.1 Physical and Chemical Properties of Carbopol Polymers

Carbopol polymers, Pemulen® polymeric emulsifiers and Noveon® polycarbophils, are polymers of acrylic acid crosslinked with polyalkenyl ethers or divinyl glycol. The polymers are flocculated powders averaging 2 to 7 microns in diameter, as determined by Coulter Counter. They are produced from primary polymer particles of about 0.2 micron average diameter. The flocculated agglomerates cannot be broken down into the ultimate particle once produced.

Each primary particle can be viewed as a network structure of polymer chains interconnected by crosslinks. Without the crosslinks, the primary particle would be a collection of linear polymer chains intertwined but not chemically bonded. These linear polymers are soluble in a polar solvent, such as water. Carbopol polymers, along with Pemulen, and Noveon polymers are all crosslinked. They swell in water up to 1000 times their original volume (and ten times their original diameter) to form a gel when exposed to a pH environment above 4.0-6.0. Since the pK_a of these polymers is 6.0 ± 0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative charges, which adds to the swelling of the polymer. Crosslinked polymers do not dissolve in water.

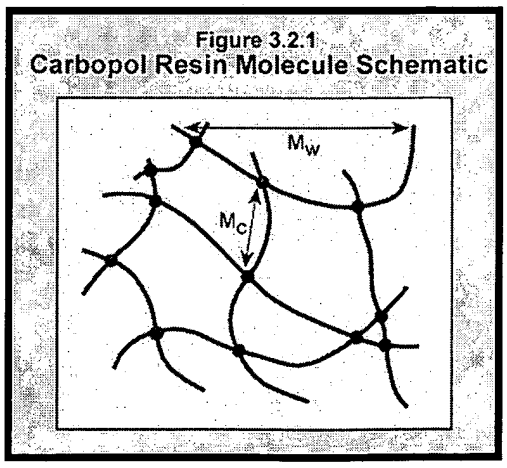
The glass transition temperature of Carbopol polymer is 105°C (221°F) in powder form. However, the glass transition temperature drops dramatically as the polymer comes into contact with water. The polymer chains start gyrating and the radius of gyration becomes bigger and bigger. Macroscopically, this phenomenon manifests itself as swelling.

3.2.2 Defining Molecular Weight for a Polymer

Polymers are heterogeneous mixtures of polymer homologues. When the molecular weight of a polymer is discussed, generally what is being referred to is actually the average molecular weight of these homologues. The molecular weight of a polymer is more fully characterized by number average molecular weight (M_n), weight average molecular weight (M_w), and viscosity molecular weight (M_v). The ratio of M_w to M_n characterizes the breadth of the molecular weight distribution, also known as "polydispersity." In order to fully characterize a polymer, both the average molecular weight and the polydispersity must be defined.

Molecular weights of crosslinked polymers are also characterized by the backbone chain length (i.e. molecular weight between adjacent crosslinks, M_c). Each network structure, (a single particle) may be viewed as a single molecule. The mass of the particle is the molecular weight, assuming all polymer chains are interconnected by chemical bonds or crosslinks. The simplest schematic view of the end-to-end molecular weight (M_w) and the molecular weight between adjacent crosslinks (M_c) can be depicted as shown in Figure 3.2.1.

Figure 3.2.1
Carbopol Resin Molecule Schematic



3.2.3 Measuring Molecular Weights

Molecular weights of linear polymers may be determined by appropriate physical measurements on very dilute solutions. Most commonly practiced methods are gel permeation chromatography (GPC) and intrinsic viscosity. Light scattering, ultracentrifugation and osmometry are also used in the determination of polymer molecular weight. However, all of these methods require the solubility of the polymer and, therefore, cannot be used to determine the molecular weight of an insoluble, crosslinked polymer, such as Carbopol polymer.

In addition, routine spectrophotometric analyses, such as ultraviolet (UV), infrared (IR) or nuclear magnetic resonance spectroscopy (NMR) can provide information about functional groups in a polymer. NMR has been used in protein analysis to develop three dimensional structural information. This method relies on good chemical shift separation between proton resonances. The primary sequence of amino acids is known through sequencing, while Nuclear Overhauser Effect (NOE) experiments are used to develop spatial information. These experiments, along with molecular modeling have allowed three-dimensional protein structures to be determined. Unfortunately, in the case of acrylic acid polymers, good chemical shift separation does not occur, rendering this method unusable on Carbopol polymers.

3.2.4 Measuring the Molecular Weights of Crosslinked Polymers

The question of quantifying the molecular weights of Carbopol polymers is quite complex. There are no simple answers due to the random crosslinked network structure of the polymers. Unfortunately, whereas some naturally occurring polymers, such as proteins, have distinct primary, secondary and tertiary structure; free radical polymers, such as Carbopol polymers, are random polymers. This, in itself, makes the polymers difficult to study because structural information is necessarily an average of many different molecules. In addition, the simple fact that these polymers are crosslinked makes direct structural studies difficult. To date, we have not been able to determine either the molecular weight of the polymer chains or the distance between crosslinks.

3.2.5 Rheological Properties and Molecular Weights

While the relationships between structure and properties have been of interest both academically and in industry[1-6] few publications have attempted to characterize the structure-property relationships of Carbopol polymers.[7-11]

Different grades of Carbopol polymers exhibit different rheological properties, a reflection of the particle size, molecular weight between crosslinks (M_c), distributions of the M_c, and the fraction of the total units which occur as terminal, i.e. free chain ends.

The molecular weights between adjacent crosslinks (M_c) are approximately inversely proportional to the crosslinker density. These may be calculated from the functionality of the crosslinking monomer, the relative ratio of acrylic acid to crosslinking monomer, and the efficiency of the crosslinking reaction, assuming negligible chain ends.[7] Alternatively, the molecular weight can be qualitatively compared to the rheological properties of a swollen gel and/or from the equilibrium swelling ratio. In simple terms, low viscosity, low rigidity polymer, such as Carbopol 941 and Carbopol 971P, have a higher M_c. Conversely, they have lower crosslinker densities. The higher the crosslinker level, the lower the equilibrium swelling ratio.

In the network theory of elasticity, the elastic modulus, G, is inversely proportional to the molecular weight between crosslinks (M_c). There have been attempts to extend the elasticity theory to swollen gels.[7,8,10] Based on this approach, Taylor calculated an M_c for Carbopol 941 in the order of several million. This number is far too high as compared to the theoretical

M_c calculated from the stoichiometry. Carnali and Naser estimated the M_c for Carbopol® 941 to be 3,300 monomer units (or 3,300 x 72 = 237,600 gm/mole) derived from a combination of dilute solution viscosity and equilibrium swelling.[9] The M_c reported for Carbopol 940 was 1,450 monomer units (or 1,450 x 72 = 104,400 gm/mole).

3.2.6 What are the Molecular Weights of Carbopol Polymers?

When Carbopol polymers have been polymerized under the same conditions, and using the same recipe as the crosslinked grades, but without the crosslinking monomer, the weight average molecular weights are in the order of about 500,000 as measured by gel permeation chromatography using linear polyacrylic acid as reference.

While the molecular weight of crosslinked Carbopol polymer between adjacent crosslinks (M_c) is in the order of thousands, the actual molecular weight is in the billions. This is because each primary particle of crosslinked Carbopol polymer can be considered as a single gigantic molecule, with the crosslinks attaching to many linear chains together. The molecular weight of such a molecule can be calculated from the size of the primary particle and the density of the polymer. The calculated molecular weight for a crosslinked Carbopol polymer with primary polymer size of 0.2 micron could be as high as 4.5 billion due to the interlinkage of many polymer chains.

3.2.7 References

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Bulletin 3

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